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Baseline cortisol and the efficacy of antiglucocorticoid treatment in mood disorders: a meta-analysis

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ABSTRACT

INTRODUCTION: Hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis and high cortisol levels have been widely reported in patients with mood disorders but previous clinical trials investigating the efficacy of antiglucocorticoid treatment in this population have reported inconsistent findings. These inconsistencies among these studies may be because not all patients with mood disorders have increased HPA axis activity and therefore might not benefit from antiglucocorticoid treatment. The aim of this meta-analysis was to investigate whether baseline cortisol levels influence the efficacy of antiglucocorticoid drugs in patients with mood disorders.

METHODS: PubMed and Scopus databases were searched systematically up to October 2018. We included studies using metyrapone, ketoconazole or mifepristone in patients with major depressive disorder, bipolar disorder and major depressive disorder with psychotic symptoms. We tested for a difference in cortisol levels between responders (a reduction equal to or greater than 30% on depression scales following antiglucocorticoid treatment) and non-responders (a reduction of less than 30% on depression scales). We performed a meta-analysis to look specifically at differences in cortisol levels in the sample of patients treated with cortisol synthesis inhibitors (metyrapone and ketoconazole) and in those treated with glucocorticoid receptor (GR) antagonist (mifepristone).

RESULTS: We were able to retrieve data from 11 of the 16 selected studies and to include 9 studies in the meta-analysis. In the overall sample (N=846), responders had similar baseline cortisol levels compared with non-responders (standardised mean difference, SMD = -0.03, 95% CI [-0.17, 0.12], $p=0.75$). In the group of patients treated with cortisol synthesis inhibitors, responders (N= 109) had significantly higher peripheral baseline cortisol levels compared with non-responders (SMD= 0.42, 95% CI [0.01, 0.83], $p=0.047$). In the group of patients treated with a GR antagonist (N= 737), both responders and non-responders had similar baseline cortisol levels (SMD= -0.09, 95% CI [-0.25, 0.07], $p=0.26$).

CONCLUSION: Our data suggest that only patients with higher cortisol levels at baseline benefit from treatment with cortisol synthesis inhibitors and support a potential role for cortisol as a predictive biomarker for treatment with cortisol synthesis inhibitors in patients with mood disorders.

Keywords: Antiglucocorticoid; Cortisol; Depression; Metyrapone; Mifepristone; Mood disorders.

1. INTRODUCTION

Given the strong evidence of hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in patients with mood disorders, several previous studies have investigated the efficacy of antiglucocorticoid treatment in this population (Maric and Adzic, 2013). However, the results of these studies investigating the efficacy of antiglucocorticoid treatments in mood disorders are inconsistent. The only extant Cochrane review focused mainly on the efficacy of mifepristone treatment in patients with psychosis (Garner et al., 2016). Therefore, this meta-analysis aimed to clarify possible reasons behind the inconsistencies of the findings reported so far.

Mood disorders are the second leading cause of disability worldwide and available treatments are not always effective (Nemeroff and Owens, 2002). It has been widely acknowledged that some patients with depression show a hyperactivation of the HPA axis (Papiol et al., 2007). Between 40% and 60% of depressed patients with mood disorders show high levels of circulating cortisol or other dysregulations of the HPA axis (Keller et al., 2017), with rates varying according to specific diagnoses. Specifically, dexamethasone test (DST) non-suppression has been reported in major depressive disorder (MDD) (up to 43%), major depressive disorder with psychotic symptoms (PMD) (up to 67%), bipolar disorder manic episode (up to 41%) and bipolar disorder mixed episode (up to 78%), (Arana and Mossman, 1988).

Hypercortisolemia may play a role in the development of treatment-resistant depression (TRD) (Jurueña et al., 2013). About 30% of patients with MDD do not respond to current antidepressant treatments, which mainly target monoamine transporters (Ionescu et al., 2015). The underlying mechanism may involve the negative effects of an excess of glucocorticoids on neuroplasticity and/or the modulation of neurotransmission. Notably, the hyperproduction of glucocorticoids (GC) decreases levels of serotonin and norepinephrine available in the synaptic cleft (Zhang et al., 2018). As a result of this evidence, several studies have tested the efficacy of antiglucocorticoids in subjects with mood disorders (Reus and Wolkowitz, 2001).

Antiglucocorticoid medications decrease the levels of glucocorticoid hormones (such as cortisol) either through inhibition of cortisol synthesis or through the antagonism of glucocorticoid receptors (GRs) (Price et al., 1996). The efficacy of the antiglucocorticoid treatment as an add-on treatment in depression still remains unclear and under investigation.

There are many methodological differences among trials, (e.g. dose of administration and the subtype of the mood disorder), which make it difficult to reach clear conclusions. Another important factor which may explain the inconsistency across the literature regards the baseline cortisol levels of the patients treated, as not all patients are hypercortisolemic. A parallel may be studies investigating anti-inflammatory drugs in patients with depression, which suggest that it is mainly subjects with high levels of inflammation who show a better response to anti-inflammatory treatment (Raison et al., 2013). Similarly, it is plausible that only patients with higher levels of cortisol will show a response to antiglucocorticoids.

The aim of this meta-analysis was to investigate the possible association between baseline cortisol levels and the efficacy of antiglucocorticoid treatment in patients with mood disorders. We considered as baseline the cortisol levels prior to each antiglucocorticoid treatment and/or prior to the effect of any stimulation (e.g. dexamethasone). We hypothesized that patients with mood disorders who respond to antiglucocorticoid treatment would have higher baseline levels of cortisol compared with patients not responding to antiglucocorticoid treatment. A secondary aim of the meta-analysis was to test whether baseline cortisol levels predict the response to antiglucocorticoid treatment differently based on the mechanism of action of the drug (cortisol inhibitors vs glucocorticoid receptor antagonist).

2. METHODS

We searched the literature published until October 2018 in PubMed and Scopus databases using the following search words and synonyms: (“mood disorders” OR “depression” OR “major depressive disorder” OR “major depressive disorder with psychotic symptoms” OR “bipolar disorder” OR “depressive symptoms” OR “treatment-resistant depression”) AND (“antiglucocorticoid” OR “glucocorticoid antagonist” OR “cortisol antagonist” OR “ketoconazole” OR “mifepristone” OR “RU-486” OR “metyrapone”) AND (“cortisol” OR “hypothalamic-pituitary-adrenal axis” OR “HPA” OR

“hyperactivity”). Articles were limited to research published in English language. One author screened the abstracts for eligibility (LG) and three authors (LG, MV and ED) assessed the articles for relevance.

2.1 Eligibility of the studies: inclusion and exclusion criteria

Inclusion Criteria: 1) mood disorders: major depressive disorder (MDD), major depressive disorder with psychotic symptoms (PMD), bipolar disorder (BD), 2) biomarker: cortisol; 3) clinical scales: Hamilton Rating Scale for Depression (HDRS, HRS, HAMD), Montgomery–Åsberg Depression Rating Scale (MADRS); 4) type of study design: placebo-controlled trial, clinical trial randomized, double-blind, single-blind, pilot study, crossover study, open-label; 5) antiglucocorticoids: ketoconazole, metyrapone, mifepristone.

Exclusion Criteria: 1) comorbidity with other psychiatric disorders or with other medical conditions; 2) lack of cortisol measurement; 3) lack of clinical outcome assessment; 4) series case studies and case reports; 5) studies investigating the effects of antiglucocorticoids which did not fit in the categories of cortisol inhibitors or GR antagonist, (this was done to reduce heterogeneity of mechanism of action).

In order to avoid the effect of the cortisol circadian rhythm, we included in the analyses afternoon and evening cortisol values when possible.

2.2 Studies overview

The initial search produced 436 results on Pubmed and 1201 results on Scopus. We selected 16 studies and we were able to retrieve data from a total of 11 studies. From the 16 studies, 3 were excluded as they were reporting data from overlapping samples with studies included (Raven et al., 1996; Gallagher et al., 2008; Block et al., 2017). From the 13 remaining studies, we were able to retrieve data from a total of 11 (Belanoff et al., 2002; Block et al., 2018; Flores et al., 2006; Jahn et al., 2004; McAllister-Williams et al., 2016; O’Dwyer et al., 1995; Paslakis et al., 2011; Thakore and Dinan, 1995; Watson et al., 2012; Wolkowitz et al., 1999; Young et al., 2004) and we were able to include 9 of these 11 studies in the meta-analysis (Belanoff et al., 2002; Block et al., 2018; Flores et al., 2006; Jahn et al., 2004; McAllister-Williams et al., 2016; O’Dwyer et al., 1995; Watson et al., 2012; Wolkowitz et al., 1999; Young et al., 2004). A description of the 13 studies is summarised in table 1.

In the meta-analysis, we included only 9 of the 11 studies, because we found in the study by Paslakis et al (2011) only one responder in a sample of 6 treated subjects and we did not find non-responders in the study by Thakore and Dinan (1995). The 9 analysed studies comprised a total of 846 subjects.

The period of drug administration varied from a minimum of 7 days to a maximum of 4 weeks. Studies investigating “ketoconazole” and “metyrapone” were mainly conducted in patients with MDD, whilst the majority of studies investigating “mifepristone” were conducted in BD and PMD patients. Among the selected articles, there was no study using mifepristone treatment in MDD patients or testing ketoconazole or metyrapone in PMD patients. See table 1.

3. ANALYSIS

3.1 Data extraction

For each study, we considered subjects treated with antiglucocorticoid treatment and did not consider the placebo group. We defined as responders (R) as depressed patients with a reduction equal to or greater than 30% on depression scales and as non-responders (NR) as those with a reduction less than 30% on depression scales. In the selected studies, the clinical scales investigating depressive outcome were: Hamilton Rating Scale for Depression (HDRS; HRS; HAMD) and the Montgomery–Åsberg Depression Rating Scale (MADRS).

From the included studies, we extracted information on: a) population (number of participants, number of responders and non-responders to antiglucocorticoid treatment, number of patients with MDD, PMD or BD); b) severity of depression (mean and SD of depression scale scores divided into responders and non-responders); c) type of antiglucocorticoid treatment; d) peripheral baseline cortisol levels (divided into responders and non-responders).

When the data were not available in the original publication, we contacted the authors.

3.2 Statistical analysis

We extracted data on the mean and standard deviation (SD) of peripheral baseline cortisol levels in responders and non-responders to antiglucocorticoid treatment. When needed, we calculated mean and SD from median and range/standard error of the mean of cortisol levels. We calculated Standardized Mean Difference (SMD), 95% confidence interval (CI), test for overall effect (Z). We assessed the heterogeneity using χ^2 test and I^2 -index. A high level of heterogeneity was considered when the p-value of the χ^2 -test was below 0.05 and I^2 -index was more than 50%.

We first analysed differences in baseline cortisol levels in responders and non-responders to antiglucocorticoid treatments in all studies. We then conducted separate analyses based on the mechanism of action of the antiglucocorticoid treatment, by testing differences in 1) baseline cortisol levels in responders and non-responders to synthesis cortisol inhibitors (metyrapone, ketoconazole) in patients with MDD; and 2) baseline cortisol levels in responders and non-responders to GR antagonist (mifepristone) in patients with PMD and BD. Statistical analyses were performed with Statistic and Data (STATA 15) program .

4. RESULTS

4.1 Baseline cortisol levels do not predict response to antiglucocorticoid treatment in patients with mood disorders

In the total number of subjects considered for the meta-analysis (N= 846), responders (N=555) have similar baseline cortisol levels compared with non-responders (N= 291), (Standardized Mean Difference (SMD) = -0.025, 95% Ci [-0.173, 0.124], p= 0.747). The heterogeneity is low ($\chi^2 = 23.00$, p value of $\chi^2 = 0.084$, $I^2 = 34.8\%$), see figure 2.

4.2 Higher baseline cortisol levels predict response to cortisol synthesis inhibitors (metyrapone, ketoconazole)

In the group of patients treated with cortisol synthesis inhibitors (metyrapone, ketoconazole) (N= 109), responders (N= 53) have significantly higher peripheral baseline cortisol levels compared with non-

responders (N= 56). (SMD=0.421, 95% CI [0.010, 0.833], $p= 0.045$). The heterogeneity is low ($\chi^2 = 4.35$, p value of $\chi^2 = 0.226$, $I^2 = 31.1\%$), see figure 3. The studies focussing on cortisol synthesis inhibitors were all investigating patients with MDD and did not include patients with PMD and BD.

4.3 Baseline cortisol levels do not predict response to glucocorticoid receptor antagonist (mifepristone)

In the group of patients treated with glucocorticoid receptor antagonist (mifepristone) (N=737), responders (N=502) and non-responders (N=235) have similar levels of baseline cortisol. (SMD= -0.092, 95% CI [-0.251, 0.068], $p= 0.261$).

The heterogeneity is low ($\chi^2 = 13.47$, p value of $\chi^2 = 0.264$, $I^2 = 18.3\%$), see figure 4. The studies focussing on glucocorticoid receptor antagonists were all investigating patients with BPMD and BD and did not include patients with MDD.

4.4 Cortisol levels after treatment do not significantly differ between responders and non-responders

In order to explore the difference in cortisol levels after treatment between responders and non-responders, a series of independent sample T-tests have been run to compare cortisol means when data after treatment were available. Only one study (Wolkowitz et al., 1999) showed a significant difference ($p= 0.032$) between responders (N= 4) and non-responders (N=5) with non-responders having lower cortisol levels at follow-up compared with responders. In the other studies, we did not find significant difference between groups after administration of ant glucocorticoid treatments.

8. DISCUSSION

Our findings did not show a significant difference in baseline cortisol levels in patients responding to ant glucocorticoid treatments when compared with patients not responding to these medications in the overall sample. However, this result changes when we run further analyses taking into account the specific mechanism of action of the drugs. In particular, we found significantly higher baseline cortisol

levels in patients responding to cortisol synthesis inhibitors compared with non-responders (all studies were in major depressive disorder patients), while we found similar baseline cortisol levels in patients responding or not to GR antagonist (all studies were in major depressive disorder with psychotic symptoms and bipolar disorder depressed patients).

The differences we detected between the group treated with cortisol inhibitors and those treated with a GR antagonist may be related to the differences in the pharmacological actions of these antiglucocorticoid drugs. Ketoconazole and metyrapone decrease cortisol levels by acting in the first and final steps of cortisol production, respectively (Becker 2001; Sampath-Kumar et al., 1997; Sonino, 1987), whereas mifepristone firstly increases cortisol levels by acting on HPA axis feedback mechanism (Kling et al., 2009) and also has an effect on the progesterone receptor. Specifically, Gallagher and colleagues found an increase of cortisol levels at day 7 after the mifepristone administration at the baseline and a significant decrease from day 7 to day 21 in patients with bipolar disorder and in patients with schizophrenia (Gallagher et al., 2008). These differences in pharmacodynamic could lead to a different effect on mineralocorticoid receptors (MRs)/GRs' balance. MRs and GRs have different affinities for cortisol. Specifically, MRs have a high affinity for this hormone and are activated by low cortisol levels, while GRs have a low affinity for this hormone and are activated only in presence of high cortisol levels (Joëls and de Kloet (1994); Kalman and Spencer (2002); Reul and de Kloet (1985)). Consequentially, administration of cortisol synthesis inhibitors in patients with high baseline cortisol levels may up-regulate MRs by lowering the levels of the steroid hormone (Jahn et al., 2004). However, mifepristone administration temporarily leads to a further increase of cortisol levels (Yuen et al., 2017) which may not help to reset the MRs/GRs balance in patients with already high cortisol levels.

However, the differences we found between the two classes of antiglucocorticoid treatments could also be explained by the differences between the populations studied. In fact, studies which used cortisol synthesis inhibitors focused on MDD patients, whereas those using the GR antagonist focused on PMD and BD patients. Previous studies suggested different patterns of HPA axis dysregulation between mood disorders and more specifically, between major depressive disorder with psychotic

symptoms and nonpsychotic major depression populations (Keller et al., 2006) that could partly account for a different response to antiglucocorticoid treatments.

Previous findings suggested a stronger efficacy of antiglucocorticoids in psychotic depressed subjects possibly related to a more pronounced HPA axis dysregulation (Schatzberg 2015). Indeed, our results show a tendency toward a greater efficacy of antiglucocorticoid treatments in patients with higher baseline cortisol levels and PMD subjects tend to have higher cortisol levels compared with non-psychotic depressed patients (Nelson and Davis, 1997). However, we did not find a significant effect of baseline cortisol levels in the efficacy of GR antagonist in PMD and BD subjects, as responders and non-responders had similar baseline cortisol levels. This may be partly due to the fact that previous literature tends to support the efficacy of mifepristone in improving psychotic rather than depressive symptoms on which our meta-analysis focused (Blasey et al., 2009). However, the mechanism associated with clinical improvement of psychotic symptoms after treatment with GR antagonists still remains unclear. Zhang and colleagues have investigated the mechanism of mifepristone in rats (Zhang et al., 2018) and they have shown that this treatment reduces depression-like behaviours induced by chronic IL-1 β administration and the effect of IL-1 β on corticosterone. Therefore, it is possible to hypothesize that mifepristone may have greater efficacy in patients presenting with high levels of inflammation rather than (or in addition to) high levels of cortisol.

One main limitation of our meta-analysis stems from the differences between methods of cortisol data collection across the studies. For example, two studies (Jahn et al., 2004; O'Dwyer et al., 1995) focused on morning blood collection, three studies (Belanoff et al., 2002; Wolkowitz et al., 1999; Young et al., 2004) focused on afternoon blood collection, one study (Flores et al., 2006) analysed blood collected between 6 pm and 1 am, and two of them focused on saliva collection in the evening (McAllister-Williams et al., 2016; Watson et al., 2012). Salivary cortisol is a valid measure for free cortisol when protein binding is an issue in serum (El-Farhan et al., 2016). Moreover, Bozovic and colleagues (2013) suggest salivary cortisol as more feasible approach to study HPA axis in research studies due to its ease of collection. However, possible confounding effects due to the subject's habits (e.g. time of food intake, smoking, etc.), may influence the results. Therefore, future studies may need to focus on the use

of salivary cortisol levels not only because the sampling would be less invasive but also because the data may be more informative.

In conclusion, we report the first evidence of a role of baseline cortisol levels in the efficacy of antiglucocorticoid treatments in patients with mood disorders. Specifically, our results show a significant effect of baseline cortisol levels in predicting the clinical response to cortisol synthesis inhibitors (ketoconazole and metyrapone) in the MDD population. Our findings support the possibility of tailored and individualised treatment for patients with mood disorders when using antiglucocorticoid treatments by implementing stratification of patients on the basis of baseline cortisol levels. Looking to the future, this stratification could help us to identify which subgroups could have the greatest benefit from cortisol synthesis inhibitors as an add-on treatment to the common antidepressants.

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Prof Young is employed by King's College London and he is honorary consultant SLaM(NHS UK). He is paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen; he is a consultant

to Johnson & Johnson. Prof Young has not shareholdings in pharmaceutical companies and is the lead investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study. Investigator-initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth, Janssen. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK); Janssen (UK).

Dr Schatzberg has served as a consultant for Alkermes, Avanir, Bracket, Epiodyne, Jazz, Lundbeck/Takeda, McKinsey, Myriad Genetics, Neuronetics, Owl, and Sage; holds equity in Corcept (co-founder), Epiodyne, Gilead, Incyte, Intersect ENT, Merck, Owl, Seattle Genetics, Titan, and Xhale; and he is listed as an inventor on pharmacogenetic and mifepristone patents from Stanford University.

9. LEGEND TO FIGURES

Figure 1. Flowchart of the searching process.

Figure 2. Antiglucocorticoid treatments in patients with mood disorders.

Figure 3. Cortisol synthesis inhibitors (Metyrapone, Ketoconazole) in MDD patients.

Figure 4. Glucocorticoid receptor antagonist (Mifepristone) in PMD and BD patients.

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Giulia Lombardo et al., 2019

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